REMARKS/ARGUMENTS

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter. The specification has been amended to delete references to embedded hyperlinks and/or browser-executable code. The reference to the page/line numbers of the amended paragraphs is based on the specification as filed, a copy of which can be obtained from the public PAIR system.

Prior to the present amendment, Claims 58-63 were pending in this application. With this amendment, Claim 58 has been amended, and Claim 63 has been canceled without prejudice. Claims 58-62 are pending after entry of the instant amendment. Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

Applicants thank the Examiner for entering the amendments of October 15, 2001, February 13, 2002, and August 21, 2002, and for considering the IDS submitted on February 13, 2002. In addition, Applicants thank the Examiner for acknowledging that the deposit of organisms under accession number ATCC 209786 under terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure is in compliance with the deposit requirement.

Double Patenting

The pending claims stand rejected under double patenting. In particular, the Examiner alleges that "there is at least one other application filed by the applicants which contains the polypeptide of SEQ ID NO: 16 which is identical to the polypeptide of SEQ ID NO: 7, and which contain possible conflicting claims". The Examiner further states that "applicant is required to point out to the Examiner all double patenting issues".

To our best knowledge, Applicants have not filed any applications having claims directed to a polypeptide of a sequence identical to SEQ ID NO: 7. Applicants believe that the Examiner reached his conclusion of the existence of possible conflicting claims based on the disclosure of

the **publications** of other U.S. applications filed by Applicants, which do not reflect the changes made in preliminary amendments in those applications.

Accordingly, Applicants request that claim rejections under double patenting be withdrawn.

Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 58-63 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is directed to non-statutory subject matter. Claim 58 is directed to an antibody that binds to the polypeptide of SEQ ID NO: 7, and such an antibody could exist in nature" (Page 4 of the instant Office Action). Applicants submit that the cancellation of Claim 63 renders the rejection of this claim moot. With respect to Claims 58-62, without acquiescing to the rejection and solely for the purpose of expediting prosecution, Applicants have amended Claim 58 to recite "isolated antibody".

According to the specification, an "isolated" antibody is "one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified: (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step" (see page 132, lines 29-38)

Thus, the claimed antibodies are distinguished over antibodies in nature and the amendment to Claim 58 (and , as a consequence, those claims dependent from the same) is supported by the specification. Accordingly, Applicants respectfully request reconsideration and

withdrawal of the present rejection.

Claims 58-63 stand rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a substantial and specific asserted utility or a well established utility." (Page 4 of the instant Office Action). Claims 58-63 are further rejected under 35 U.S.C. §112, first paragraph allegedly because one skilled in the art would not know how to use the claimed invention "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." (Page 8 of the instant Office Action). The Examiner specifically notes that "the utilities that pertain solely to nucleic acids ... would not convey to the encoded protein" and therefore concludes that no asserted utility is specific for PRO274 protein. The Examiner also asserts that the data showing the amplification of the nucleic acids encoding PRO274 is not indicative of a use of the encoded polypeptide as a diagnostic or therapeutic agent. Further, the Examiner alleges that since the data are not corrected for aneuploidy, and because it does not necessarily follow that an increase in gene copy number results in increased gene expression, the data do not support the implicit assertion that PRO274 can be used as a cancer diagnostic. The Examiner further quotes exemplary references like Pennica *et al* and Gygi *et al.* to show that "it does not necessarily follow that an increase in gene copy numbers results in increased gene expression and increased protein expression, such that antibodies would be useful diagnostically or as target for cancer drug development." For the reasons outlined below, Applicants respectfully disagree.

Applicants submit that the cancellation of Claim 63 renders the rejection of this claim moot. With respect to Claims 58-62, Applicants submit, as discussed below, that not only has the PTO not established a *prima facie* case for lack of utility, but that the antibodies of Claims 58-62 possess a specific and substantial asserted utility.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "[t]he basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient**, at least with regard to defining a "'substantial'" utility.'" (M.P.E.P. §2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, §2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. §2107 II (B) (1) (ii)) Such a standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

The PTO also sets forth the evidentiary standard as to utility rejections. In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. §101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. *In re* Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

Proper Application of the Legal Standard

As discussed below under the section on "priority", Applicants rely on the gene amplification data for patentable utility for the PRO274 gene and the PRO274 protein and antibodies thereof.

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 114 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9, including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control. Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9. Further, Example 114

explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein one unit corresponds to one PCR cycle or approximately a 2-fold amplification relative to control, two units correspond to 4-fold amplification, 3 units to 8-fold amplification etc. PRO274 showed approximately 1.06-1.24 ΔCt units which corresponds to $2^{1.06}$ -$2^{1.24}$ fold (more than 2 fold) amplification in three types of human primary lung tumors, which is significant and thus the PRO274 gene has utility as a diagnostic marker of lung cancer.

It is well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.,* non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

The attached Declaration by Audrey Goddard clearly establishes that the TaqMan real-time PCR method described in Example 114 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO274 is a diagnostic marker of human lung cancer.

Secondly, regarding the Examiner's point that "none of [the] asserted utilities is specific for the disclosed PRO274 proteins or antibodies," Applicants submit, as

discussed below, that the Examiner has not established a *prima facie* case for lack of utility for PRO274 polypeptides and their antibodies.

A *prima facie* case of lack of utility has not been established

The Examiner bases the assertion, that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression, on exemplary literature reports like Pennica *et al.* and Gygi *et al.* and hence concludes that the PRO274 polypeptides and their antibodies lack utility.

According to the Examiner, Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, ... In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Firstly, Applicants draw attention to Pennica's showing that "a correlation between DNA amplification and over-expression exists for the *WISP*-1 gene"in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaches nothing of the correlation between gene amplification and polypeptide over-expression in general.

Further, the Examiner cites the Gygi *et al.* reference to establish that "even if gene amplification correlates with increased transcription, it does not always follow that protein levels are also amplified." The Examiner adds that "Gygi *et al.* studied 150 proteins... and found no strong correlation between proteins and transcript levels." Applicants respectfully traverse and point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in

accurately predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). Contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). For example, as shown in Figure 5, the mRNA abundance of **250-300** copies /cell correlates with the protein abundance of **500-1000** x 10^3 copies/cell. The mRNA abundance of **100-200** copies/cell correlates with the protein abundance of **250-500** x 10^3 copies/cell (emphasis added). Therefore, high levels of mRNA **generally** correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data, meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Applicants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, as observed for the *WISP-2* or the *abl* genes, is typical. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.*, a correlation between DNA amplification: polypeptide over-expression was observed in the case of *WISP-1* and similarly, in Gygi *et al.*, **most genes** showed a correlation between increased mRNA : translated protein. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in

malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.,* (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared

the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO274 proteins and nucleic acids have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an

expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO274 polypeptide, for example, in detecting over-expression or absence of expression

of PRO274. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed polypeptides.

Hence, these data clearly support a role of PRO274 as a lung tumor marker. Accordingly, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

Claim Rejections – 35 U.S.C. §112, second paragraph

A. Claim 61 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner alleges that it is not understood "how an antibody can be both an 'antibody' and a 'fragment'."

Applicants submit that the definition of "antibody" includes "antibody fragments" and the definition has been well-defined on page 308, line 22 onwards. As the Examiner is aware, Applicants can be their own lexicographer and hence Claim 61 is definite and this rejection should be withdrawn.

B. Claims 58-63 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. In particular, The Examiner alleges that "the specification, does not define the term 'specifically binds' the polypeptide, and it is not clear what this means, and it is not clear what the difference in scope between 'bind' and 'specifically binds' is". Applicants respectfully traverse this rejection.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled Claim 63 and have amended Claim 58 to recite "specifically binds". Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Accordingly, one skilled in the art would knows what the scope of the invention is.

Accordingly, Applicants respectfully request that this rejection to claims be withdrawn.

Priority

Applicants submit that they rely on the gene amplification assay for patentable utility which was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which has been claimed in this application. Accordingly, the present application is entitled to at least an effective filing date of **February 11, 2000.** In support, Applicants enclose herewith pages 138-163, describing the gene amplification assay (Example 26), of WO 01/53486, corresponding to PCT application, PCT/US00/03565.

Claim Rejections – 35 U.S.C. §102(b)

Claims 58-63 are rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270 (dated July 14, 2000). Applicants respectfully traverse this rejection.

As the claims pending in this application are entitled to the priority date of PCT/US00/03565, filed **February 11, 2000,** the article by Ho *et al.* is not prior art and hence, this rejection should be withdrawn.

Claim Rejections – 35 U.S.C. §103(a)

Claims 59-62 are rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Immunology, The Immune System in Health and Disease, Third Edition, Janeway, And Travers, Ed., 1997. Applicants respectfully traverse this rejection.

As discussed above, the article by Ho *et al.* is not prior art to the pending claims of the present application. As a result, this rejection should be withdrawn.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below. Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2630 P1C9**).

Respectfully submitted,

Date: September 14, 2004

By: _____
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